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PATENT APPLICATION TRANSMITTAL LETTER UNDER 37 C.F.R. §1.53(b)

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Commissioner for Patents
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Alexandria, VA 22313-1450

Transmitted herewith for filing is the patent application of

Inventors(s): Anchel SCHWARTZ and Asher MAIMON,

For: **A CRYSTALLIZATION METHOD FOR PURIFICATION OF CALCIPOTRIENE**

Enclosed are:

1. **14** sheets of specification, **5** sheets of claims, and **1** sheet of abstract.

2. **-0-** sheets of drawing.

3. Related Applications:

This application claims the benefit of U.S. Provisional Application Serial Number 60/427,258, filed November 18, 2002 which is incorporated herein by reference.

4. The filing fee has been calculated as shown below:

	NUMBER FILED	NUMBER EXTRA*	RATE ($)	FEE ($)
BASIC FEE				770.00
TOTAL CLAIMS	27 - 20 =	7	18.00	126.00
INDEPENDENT CLAIMS	5 - 3 =	2	84.00	168.00
MULTIPLE DEPENDENT CLAIM PRESENT			280.00	0.00
*Number extra must be zero or larger			TOTAL	1,064.00
If applicant is a small entity under 37 C.F.R. §§ 1.9 and 1.27, then divide total fee by 2, and enter amount here.			SMALL ENTITY TOTAL	0.00

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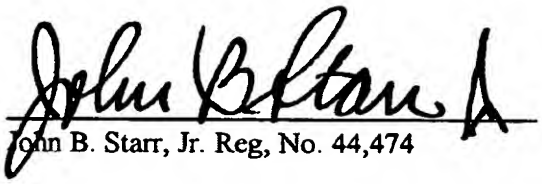
5. Please charge the required application filing fee of **$1,064.00** to the deposit account of **Kenyon & Kenyon**, deposit account number **11-0600**.

6. The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to the deposit account of **Kenyon & Kenyon**, deposit account number **11-0600**, during the entire pendency of this application:

   A. Any additional filing fees required under 37 C.F.R. § 1.16;
   B. Any additional patent application processing fees under 37 C.F.R. § 1.17;
   C. Any additional patent issue fees under 37 C.F.R. § 1.18;
   D. Any additional document supply fees under 37 C.F.R. § 1.19;
   E. Any additional post-patent processing fees under 37 C.F.R. § 1.20; or
   F. Any additional miscellaneous fees under 37 C.F.R. § 1.21.

7. A duplicate copy of this sheet is enclosed.

Dated: November 18, 2003

By: 
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What is claimed is,

1. A method of crystallizing calcipotriene comprising the steps of:

a) providing a solution of a starting calcipotriene in a first solvent selected from: lower alkyl alcohols, lower aliphatic ketones, alkyl esters of lower carboxylic acids, and cyclic ethers,

b) combining, with mechanical agitation, the provided solution with from about 1 to about 100 volumes of a second solvent,

c) cooling the combination to a temperature of less than about -10°C, and

d) isolating calcipotriene from the resulting suspension, wherein

when the first solvent is a cyclic ether the second solvent is methyl formate, when the first solvent is a lower alkyl alcohol the second solvent is a lower hydrocarbon, and when the first solvent is a lower dialkyl ketone, the second solvent is methyl formate.

2. The method of claim 1 wherein the provided solution is combined with about 30 volumes of second solvent.

3. The method of claim 1 wherein the mechanical agitation is mechanical stirring at 210 to 260 RPM.

4. The method of claim 1 wherein the first solvent is a cyclic ether and the second solvent is methyl formate.

5. The method of claim 4 wherein the cyclic ether is tetrahydrofuran.

6. The method of claim 1 wherein the first solvent is *iso*-propyl alcohol and the second solvent is hexane.

7. The method of claim 1 wherein the first solvent is acetone and the second solvent is methyl formate.

8. The method of claim 1 wherein the combination is cooled at a cooling rate of less than about 40° C per hour.

9. A method of making calcipotriene having a reduced level of impurities comprising the steps of:

a) providing a solution of starting calcipotriene in a first solvent selected from: lower alkyl alcohols, lower aliphatic ketones, alkyl esters of lower carboxylic acids, and cyclic ethers,

b) combining the provided solution, with controlled mechanical agitation, with from about 1 to about 100 volumes of a second solvent,

c) cooling the combination to a temperature of less than about -10°C at a cooling rate between about 10° and about 40° C per hour, and

d) isolating from the resulting suspension calcipotriene having a reduced level of impurities, wherein when the first solvent is a cyclic ether the second solvent is methyl formate, when the first solvent is a lower alkyl alcohol the second solvent is a lower hydrocarbon, and when the first solvent is a lower dialky ketone, the second solvent is methyl formate.

10. The method of claim 9 wherein the controlled mechanical agitation is stirring at about 210 to about 260 RPM.

11. The method of claim 9 wherein the provided solution is combined with about 30 volumes of second solvent.

12. The method of claim 9 wherein the first solvent is tetrahydrofuran and the second solvent is methyl formate.

13. The method of claim 9 wherein the first solvent is *iso*-propanol and the second solvent is hexane.

14. The method of claim 9 wherein the first solvent is acetone and the second solvent is methyl formate.

15. The method of claim 9 wherein the calcipotriene having a reeduced level of impurities has an average nominal particle size of about 15μ to about 40μ.

16. A method of making purified calcipotriene having a reduced level of impurities and a reduced level of residual first process solvent comprising the steps of:

a) providing a solution of starting calcipotriene in a first solvent selected from: lower alkyl alcohols, lower aliphatic ketones, alkyl esters of lower carboxylic acids, and cyclic ethers,

b) combining the provided solution, with controlled mechanical agitation, with from about 1 to about 100 volumes of a second solvent,

c) cooling the combination to a temperature of less than about -10°C at a cooling rate between about 10° and about 40° C per hour,

d) isolating from the resulting suspension calcipotriene having a reduced level of impurities, wherein when the first solvent is a cyclic ether the second solvent is methyl formate, when the first solvent is a lower alkyl alcohol the second solvent is a lower hydrocarbon, and when the first solvent is a lower dialky ketone, the second solvent is methyl formate,

e) suspending the isolated calcipotriene in a suspending volume of methyl formate at a temperature between about -10° and about 20° C with controlled agitation for a suspension time, and

f) isolating from the suspension purified calcipotriene having a reduced level of impurities and a reduced level of first process solvent.

17. The method of claim 16 wherein the calcipotriene having a reduced level of impurities and reduced level of first process solvent has a nominal average particle size of about 15μ to about 40μ.

18. The method of claim 16 wherein the controlled agitation is stirring at about 210 to about 260 RPM.

19. The method of claim 16 wherein the provided solution is combined with about 30 volumes of second solvent.

20. The method of claim 16 wherein the suspension time is between about 1 and about 5 hours.

21. The method of claim 16 wherein the first solvent is tetrahydrofuran and the second solvent is methyl formate.

22. The method of claim 16 wherein the first solvent is *iso*-propanol and the second solvent is hexane.

23. The method of claim 16 wherein the first solvent is acetone and the second solvent is methyl formate.

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24. ~~25.~~ Calcipotriene having a reduced level of impurities prepared by a process comprising the steps of:

a) providing a solution of starting calcipotriene in a first solvent selected from: lower alkyl alcohols, lower aliphatic ketones, alkyl esters of lower carboxylic acids, and cyclic ethers,

b) combining the provided solution, with controlled mechanical agitation, with from about 1 to about 100 volumes of a second solvent,

c) cooling the combination to a temperature of less than about -10°C at a cooling rate between about 10° and about 40° C per hour, and

d) isolating from the resulting suspension the calcipotriene having a reduced level of impurities, wherein when the first solvent is a cyclic ether the second solvent is methyl formate, when the first solvent is a lower alkyl alcohol the second

solvent is a lower hydrocarbon, and when the first solvent is a lower dialky ketone, the second solvent is methyl formate.

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~~26.~~ 24 The calcipotriene of claim ~~25~~ wherein the process further comprises the steps of:

e) suspending the isolated calcipotriene in a suspending volume of methyl formate at a temperature between about -10° and about 20° C with controlled agitation for a suspension time, and

f) isolating from the suspension the purified calcipotriene having a reduced level of impurities, wherein the purified calcipotriene also has a reduced level of first process solvent.

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~~27.~~ A pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and calcipotriene having a reduced level of impurities wherein such calcipotriene is prepared in by a method comprising the steps of:

a) providing a solution of starting calcipotriene in a first solvent selected from: lower alkyl alcohols, lower aliphatic ketones, alkyl esters of lower carboxylic acids, and cyclic ethers,

b) combining the provided solution, with controlled mechanical agitation, with from about 1 to about 100 volumes of a second solvent,

c) cooling the combination to a temperature of less than about -10°C at a cooling rate between about 10° and about 40° C per hour, and

d) isolating from the suspension calcipotriene having a reduced level of impurities, wherein when the first solvent is a cyclic ether the second solvent is methyl formate, when the first solvent is a lower alkyl alcohol the second solvent is a lower hydrocarbon, and when the first solvent is a lower dialky ketone, the second solvent is methyl formate.